REMARKS

Reconsideration of the present application is respectfully requested in view of the above amendments and the following remarks. Claims 90-178 are currently pending and under examination in the application. Notwithstanding the grounds for rejection, and without prejudice to pursuing the encompassed subject matter in related divisional, continuation, or continuation-in-part application, by present amendment, claims 95, 98, 99, 101, 103-112, 125, 140, 165, and 166 are canceled, and claims 90-94, 96, 97, 100, 102, 113-120, 123, 124, 126-128, 130-133, 136, 138, 142, 151, 152, 154, 157, 167, and 168 are amended to more particularly point out and distinctly claim certain embodiments of the Applicant's invention. No new matter is added by the present amendment. Support for the present amendment can be found in the claims and in the specification as originally filed, for example, on page 4, lines 19-20; page 9, lines 21-23; page 9, lines 25-28; page 11, lines 8-11; page 38, lines 20-31; page 39, lines 10-11.

REJECTIONS UNDER 35 U.S.C. § 103

Claims 90-178 stand rejected under 35 U.S.C. § 103(a) as allegedly obvious over Barbera-Guillem *et al.* in view of Tanke *et al.* In particular, the Action agrees that Barbera-Guillem *et al.* do not teach a diverse population of 30 or more unique labels, but asserts that a person or ordinary skill in the art would arrive at the presently claimed subject matter with a reasonable expectation of success by adapting the combinatorial ratio labeling of Tanke *et al.* to the polynucleotide based, quantum dot probes of Barbera-Guillem *et al.*

Applicant respectfully traverses this rejection and submits that the instant claims satisfy the requirements of non-obviousness under 35 U.S.C. § 103. For clarity, Applicant has amended the claims to more precisely set forth one aspect of the invention. Further, Applicant submits that the Examiner has not established a *prima facie* case of obviousness with respect to the presently claimed subject matter. *See In re Mayne*, 104 F.3d 1339 (Fed. Cir. 1997) (The

USPTO has the burden of showing a *prima facie* case of obviousness). At a minimum, it must be demonstrated that the combined references teach or suggest all the claim features, and even assuming, *arguendo,* that the combination of references teaches each claim feature, the Action must provide an explicit, apparent reason to combine these features in the fashion claimed by the Applicant with a reasonable expectation of success. *See KSR v. Teleflex, Inc.,* No 04-1350 at 4, 14 (U.S. Apr. 30, 2007) ("A patent composed of several elements is not proved obvious merely by demonstrating that each element was, independently, known in the prior art"). Here, neither of the cited references, alone ***or in combination***, teach or suggest, in pertinent part, a diverse population of 30 or more uniquely labeled, target-specific polynucleotide probes that each have a detectable signal that distinguishes it from the other polynucleotide probes of the population, wherein each of the probes comprises a target-specific region and a region having a plurality of genedigits *linked together in a unique combination*, wherein at least two of the genedigits *differ in nucleotide sequence*, each of which *different* genedigit is attached to a *unique* label via a corresponding anti-genedigit sequence.

Barbera-Guillem *et al.* fail to teach or suggest each feature of the instant claims. In particular, Barbera-Guillem *et al.* fail to teach or suggest a mixture of 30 or more uniquely labeled polynucleotide probes, wherein each unique probe comprises a plurality of genedigits (*i.e.,* discrete nucleotide sequences) *linked together in a unique combination*, wherein at least two of the genedigits *differ in nucleotide sequence*, and wherein each *different* genedigit is attached to a *unique* label via hybridization to a corresponding nucleotide sequence. In fact, Barbera-Guillem *et al.* are entirely silent as to the possibilities of linking together in a ***linear*** fashion multiple, discrete nucleotide sequences (*i.e.,* genedigits), some of which may be the same or different, and attaching a unique label monomer to each distinct nucleotide sequence, thereby creating a *single polynucleotide molecule* having a distinct, linear pattern of detectable labels attached thereto. Barbera-Guillem *et al.* merely teach nanocrystal embodiments that have attached thereto at least one probe that contributes to a three-dimensional (*i.e.,* non-linear) dendrimer formation, and which provides no functional equivalent to the unique, linear

arrangement of the presently claimed gene-digit/anti-genedigits. The non-linear dendrimer formation of Barbera-Guillem *et al.*, therefore, does not allow for more than one *uniquely detectable* signal at a given primary nanocrystal.

In contrast to Barbera-Guillem *et al.*, the instant application teaches that the modular design (*i.e.,* linear ordering) of such genedigit/label combinations allows for flexibility in the number of unique labels that may be generated (*see, e.g.,* page 38, lines 29-31 of the specification). For example, by linking together various combinations of genedigit sequences in a ***linear*** fashion (and the complementary anti-genedigit/unique label monomers) as part of a single polynucleotide molecule, even when repeatedly using one or more of the same genedigit sequences, a large number of unique labels can be generated, including 200, 500, 2,000, 5,000, $1x10^4$, $3x10^4$, $1x10^5$ or more *unique* labels (*see, e.g.,* page 40, lines 6-11 of the specification), which, due to the unique, linear ordering of the label monomers in each polynucleotide, can be read and distinguished from each other similar to a bar code. Given the deficiencies of the molecular probes of Barbera-Guillem *et al.* in this regard, this reference fails to teach each feature of the instant claims.

Tanke *et al.* does not remedy the defects in Barbera-Guillem *et al.*, as this reference also fails to teach or suggest a polynucleotide molecule having a plurality of genedigits *linked together in a unique combination*, wherein at least two of the genedigits *differ in nucleotide sequence*, wherein each of the *different* genedigit is attached to a *unique* label via hybridization to a corresponding nucleotide sequence. Since neither of the references, alone ***or in combination***, teach each feature of the instant claims, Applicant submits that the cited references fail to provide the minimal requirements of *prima facie* case of obviousness over the presently claimed subject matter.

In addition, the cited references provide no motivation to combine, or capability of combining, their respective teachings in arriving at the presently claimed subject matter at all, let alone with a reasonable expectation of success. For one, as previously detailed on the record, Applicant respectfully disagrees with the Examiner's assertion that the combined binary ratio

labeling method of Tanke *et al.* is technically suitable, or adaptable to, the method of Barbera-Guillem *et al.* (*see* the Action, page 4). Nonetheless, even assuming, *arguendo*, that the two methods are technically adaptable or otherwise combinable, a combination of the two methods would not lead to the presently claimed subject matter. Indeed, a combination of Barbera-Guillem *et al.* and Tanke *et al.* would lead to something else entirely, since neither reference, alone ***or in combination***, teaches or suggests *a polynucleotide probe* having a target-specific region and a region comprising plurality of genedigits *linked together in a unique combination*, wherein at least two of the genedigits *differ in nucleotide sequence*, and wherein each *different* genedigit is attached to a *unique* label via hybridization to a corresponding nucleotide sequence. Rather, the method of Barbera-Guillem *et al.*, even if utilized according to the labeling method of Tanke *et al.*, simply does not allow for *linear*, combinatorial arrangements of labels without entirely altering the basic structure of the molecular probe subunits described therein. As such, a person of ordinary skill in the art would have had to embark on a whole new line of experimentation to arrive at the presently claimed polynucleotide labels, which would require modifying the probes of Barbera-Guillem *et al.* in a manner that is not taught or suggested by any of the references of record. Absent such experimentation, Applicant respectfully submits that the only way the Examiner could arrive at the presently claimed subject matter from combination of Barbera-Guillem *et al.* and Tanke *et al.* is by relying on the disclosure in the instant specification, and, thus, by relying on impermissible hindsight.

Applicant also notes that the European Union has recently allowed claims almost identical to the claims of the instant application, as presently amended, determining that this subject matter is both novel and inventive over the references cited in that jurisdiction. A copy of the EP allowed claims is enclosed.

In view of the amendments and remarks provided herein, Applicant submits that the instant claims satisfy the requirements of non-obviousness over the cited references, and kindly requests reconsideration and withdrawal of the rejection under 35 U.S.C. § 103(a).

Applicant believes that all of the claims in the application are allowable. Favorable consideration and a Notice of Allowance are earnestly solicited.

The Director is authorized to charge any additional fees due by way of this Amendment, or credit any overpayment, to our Deposit Account No. 19-1090.

Respectfully submitted,

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Enclosure:
Allowed EP claims for Seed IP reference 690142.401EP

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New Claims

1. A diverse population of uniquely labeled probes, comprising thirty or more target-specific nucleic acid probes, each attached to a unique label bound to a nucleic acid, each nucleic acid probe being a nucleic acid molecule comprising a target-specific region and a region comprising genedigits, said genedigits being nucleic acid regions of predetermined nucleotide sequences that are specifically bound by complementary anti-genedigit nucleotide sequences, each said anti-genedigit nucleotide sequence being attached to a label monomer or a combination of label monomers, wherein the population is in solution, and wherein the label has a detectable signal that is fluorescence, luminescence, colorimetric, voltage, current, or a magnetic field.

2. The diverse population of claim 1, comprising thirty or more target-specific nucleic acid probes, wherein each nucleic acid probe comprises four or more genedigits, said genedigits being nucleic acid regions of predetermined nucleotide sequence that are specifically bound by complementary anti-genedigit nucleotide sequences, each said anti-genedigit nucleotide sequence being attached to a label monomer or a combination of label monomers, wherein the population is in solution, and wherein the label has a detectable signal that is fluorescence, luminescence, colorimetric, voltage, current, or a magnetic field.

3. The diverse population of any one of claims 1 to 2, wherein each probe is synthetic.

4. The diverse population of any one of claims 1 to 3, wherein each probe is DNA attached to a bridging nucleic acid.

5. The diverse population of any one of claims 1 to 4, wherein said label monomers are attached to dendrimers.

6. The diverse population of any one of claims 1 to 5 wherein the genedigits are DNA.

7. The diverse population of any one of claims 1 to 6, wherein the probes comprise tags.

8. The diverse population of claim 7, wherein the tags are biotin tags.

9. The diverse population of any one of claims 1 to 8, wherein a quantum dot is used as a label monomer.

10. The diverse population of any one of claims 1 to 8, wherein a fluorophore is used as a label monomer.

11. The diverse population of any one of claims 1 to 10, comprising 50, 100, 200, 500, 1,000, 2,000, 5,000, 1×10^4, 3×10^4, 1×10^5 or more different nucleic acid probes.

12. The diverse population of any one of claims 1 to 11, wherein the nucleic acid probes are separated from one another.

13. The diverse population of claim 12, wherein the nucleic acid probes are spread on a two-dimensional surface.

14. The diverse population of any one of claims 1 to 13, wherein one or more of the target-specific probes is hybridized to an analyte and wherein the signal from the hybridized target-specific probe uniquely identifies the analyte.

15. A method of detecting a nucleic acid analyte, comprising:

(a) contacting a mixture of nucleic acid analytes with the diverse population of uniquely labeled probes of any one of claims 1 to 11 under conditions sufficient for hybridization of the probes to target nucleic acid analytes, and

(b) measuring the resulting signal from one or more of the target specific probes hybridized to an analyte, where the signal uniquely identifies the analyte.

16. A method of quantifying a nucleic acid analyte, comprising:

(a) contacting a mixture of nucleic acid analytes with the diverse population of uniquely labeled probes of any one of claims 1 to 11 under conditions sufficient for hybridization of the probes to target nucleic acid analytes;

(b) measuring the resulting signal from one or more of the target specific probes hybridized to an analyte, where the signal uniquely identifies the analyte, thereby identifying the target nucleic acid analyte; and

(c) counting the individual molecules of the nucleic acid analyte in the sample,

thereby quantifying the nucleic acid analyte.

17. The method according to any one of claims 15 and 16, wherein the position of the label monomer or combination of label monomers is used as a distinguishing characteristic.

18. The method according to any one of claims 15 to 17, wherein the nucleic acid probes are subjected to a flow-stretching technique, to a receding meniscus technique, to an electrostretching technique, or to constriction in the flow of a liquid containing said nucleic acid probes in conjunction with an oscillating electric field.